

**Venous thrombosis at altitudes presents with distinct biochemical profiles: A comparative study from Himalayas to plains**

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**SUPPLEMENTAL DATA**

## SUPPLEMENTAL METHODS

### Patient diagnosis and management

Patients with initial VTE symptoms were investigated for confirmatory diagnoses. DVT was the commonest presentation and was suspected when any patient presented with swelling of lower limb, not explained by any other local cause. Diagnosis was further confirmed by Doppler examination. Location of the DVT was confirmed as distal (infra popliteal) or proximal (supra popliteal). Echocardiography followed by CT pulmonary angiography were done on DVT associated PTE patients from HA with sudden onset dyspnea tachycardia, hypoxia or features of pulmonary infarction in the form of cough, pleuritic chest pain or hemoptysis. Patients who showed evidence of thrombus in the branch pulmonary arteries that were thrombolysed with rtPA (100mg infusion). However, massive PTE with hypotension was not present in any of the PTE cases. All DVT patients were treated with low molecular weight heparin (LMWH) and further switched over to vitamin K antagonists (VKA), an oral anti-coagulant (OAC). A follow up for six months had shown recanalization of the deep veins and resolution of the DVT. None of these patients developed evidence of chronic thromboembolic pulmonary arterial hypertension.

Patient suspected to CVT with headache and focal neurologic deficits like hemiparesis, aphasia, ataxia, hemianopia underwent MRI and MR venogram. CVT patients had either papilledema on optic fundus examination or focal neurologic deficits (hemiparesis, aphasia, and ataxia) with cerebellar signs. All patients were managed conventionally with cerebral decongestive measures. On a follow-up of one year patients had full functional recovery; however, three patients had residual hemiparesis with grade 3 power. Doppler examination of the portal venous system was done in suspected PVT patients with pain abdomen, hepatosplenomegaly or evidence of

gastrointestinal bleed. PVT patients were managed with LMWH and OAC. A follow of six months showed complete recovery.

#### **Detailed laboratory investigation**

Clinical profile recording was performed for each patient including demographic (age, serving altitude and duration) and laboratory investigations. Laboratory investigations included comprehensive evaluation of 54 parameters related to hemostasis in the enrolled patients after Factor V Leiden (1691G/A, rs6025) and prothrombin (20210G/A, rs1799963) polymorphisms screening in order to rule out any possible mutations predisposing towards prothrombotic state. Hematology details comprised measurement of hemoglobin, red blood cell count, and platelet counts using MS4 hematology analyzer (Melet Schloesing, US). Complete lipid profile was done and included total cholesterol measurement along with triglyceride, HDL, and LDL estimation using automated biochemistry analyzer (Siemens Healthcare Diagnostics, Germany). PT, aPTT, TT, fibrinogen, D-dimer, VWF, TAT, and PAP were estimated to evaluate the coagulation profile. Semi-automated coagulation analyzer from Diagnostica Stago, France, was used for coagulation screening (PT, aPTT, TT, fibrinogen, D-dimer, and VWF antigen). TAT and PAP antigen level were evaluated using colorimetric assay. The complete thrombophilia screening comprised Protein C and S deficiency, Antithrombin III (AT) deficiency, and clotting factors (V, VII, VIII, X). Protein C and Protein S activity were determined by commercially available STACLOT kits on an automated STA compact analyzer (Diagnostica Stago, France) and test results for Protein C and Protein S were expressed as relative percentages. The expected normal activity of Protein C is 70–130% and that for Protein S is 65–140%. The quantification of AT was done using STACHROM AT III kit on STA analyzer. Normal values for AT ranged from 80 to 120% and for the clotting factors (V, VII, VIII and X) ranged from 95 to 150%. Activated

protein C resistance (APCR) in plasma was measured using the Stago Diagnostica kit. Mutational analysis for Factor V Leiden (1691G/A, rs6025) and prothrombin (20210G/A, rs1799963) were performed by Restriction Fragment Length polymorphism (RFLP) method. Plasma soluble markers for platelet activation (P-selectin, CD40 ligand, and Platelet factor 4) were estimated. Intracellular adhesion molecule1 (ICAM 1), vascular cell adhesion molecule 1 (VCAM 1), vascular endothelial growth factor (VEGF), vascular endothelial growth factor receptor 3 (VEGFR 3/FLT 4), toll like receptor 2 (TLR 2), and E-selectin were measured as markers for endothelial cell activation and angiogenesis. All markers were estimated using Sandwich ELISA as per manufacturer protocols (R&D systems, MN, USA). Absorbance was taken using Synergy hybrid H4 multimode reader (BioTek, VT, US) and concentration was presented in ng/mL. E-selectin was measured using bead based flow cytometry assay (eBiosciences, USA). Additionally, plasma concentrations of heat shock protein 70 and hypoxia inducing factor-1 $\alpha$  were analyzed to evaluate the extent of stress at HA (hypoxia at HA) by sandwich ELISA and oligo-based colorimetric assay (R&D systems, MN, USA) respectively. Furthermore, panel of 18 different inflammatory chemokines and cytokines were measured in plasma of the patients using bead based flow cytometry assay (eBiosciences, USA).

84 **SUPPLEMENTAL TABLES:**

85

86 **Table S1. Concentration of the parameters investigated in HAP and SLP groups.**

	<b>HAP, median (IQR)  n=53</b>	<b>SLP, median (IQR)  n=45</b>	<b><i>p</i></b>
<b><i>Hematology</i></b>			
Hemoglobin (mg/dl)	15.4 (14.8 – 16.85)	14.8 (14.1 – 15.75)	0.012
Red blood cells (x10 <sup>6</sup> / Cumm)	5.29 (4.9 – 5.63)	4.91 (4.55 – 5.39)	0.015
Platelets (x10 <sup>3</sup> /Cumm)	247 (198 – 303)	218 (175 – 248)	0.001
Total leucocyte (/Cumm)	6500 (5650 – 8050)	6000 (5300 – 6750)	0.081
<b><i>Lipid profile</i></b>			
Total cholesterol (mg/dl)	168 (149 – 196)	159 (126 – 207.5)	0.828
Triglyceride (mg/dl)	165 (125 – 251)	180 (108.5 – 235.5)	0.7080
High density lipoprotein (mg/dl)	41 (35 – 43.5)	42 (35 – 53)	0.075
Low density lipoprotein (mg/dl)	85 (68 – 104.5)	81 (54 – 112)	0.461
<b><i>Coagulation profile</i></b>			
Prothrombin time (s)	14 (13.35 – 15.1)	14 (13.7 – 15.05)	0.193

Activated partial thromboplastin time (s)	39.65 (35.88 – 43.88)	40.5 (36.6 – 43.4)	0.554
Thrombin time (s)	18.7 (18.2 - 19.8)	18.9 (18.4 – 19.9)	0.092
Fibrinogen (mg/ml)	272 (223 - 345)	239 (203.5 – 288)	0.023
D-dimer (mg/l)	0.51 (0.25 – 0.9)	0.25 (0.17 – 0.62)	0.015
VWF Antigen (%)	144 (121.5 – 180)	127 (110 – 143.5)	0.004
Thrombin-anti-thrombin complex (ng/ml)	0.13 (0.1 - 0.2)	0.09 (0.08 - 0.13)	0.0007
Plasmin-anti-plasmin complex (ng/ml)	0.38 (0.34 - 0.43)	0.34 (0.3 - 0.39)	0.001
<b><i>Thrombophilia profile</i></b>			
Protein C (%)	75 (38.5 – 114)	86 (44 – 117)	0.649
Protein S (%)	62 (36.5 – 83)	64 (40 – 94)	0.151
Anti-thrombin (%)	89 (65 – 101)	86 (76 – 104.5)	0.335
Factor V (%)	113 (85 – 140.5)	92 (73 – 114.5)	0.010
Factor VII (%)	115 (74 – 144.5)	97 (71.5 – 111.5)	0.007
Factor VIII (%)	137 (76.5 – 154.5)	105 (93 – 120.5)	0.026
Factor X (%)	125 (101.5 – 155.5)	110 (86.5 – 133)	0.002
<b><i>Platelet activation molecules</i></b>			

CD40 Ligand (ng/ml)	8.64 (7.52 - 11.49)	6.14 (3.36 - 7.06)	<0.0001
P-selectin (ng/ml)	61.23 (52.09 - 124.3)	32.95 (22.34 - 66.34)	<0.0001
Platelet factor 4 (ng/ml)	60.91 (58.69 - 62.93)	51.18 (45.93 - 54.9)	<0.0001
<b><i>Endothelial cell activation molecules</i></b>			
Intracellular adhesion molecule type-1 (ng/ml)	47.43 (42.39 - 53.95)	38.23 (32.73 - 44.33)	<0.0001
Vascular cell adhesion molecule type - 1 (ng/ml)	27.68 (24.23 - 32.35)	15.83 (13.24 - 17.63)	<0.0001
Vascular endothelial growth factor (ng/ml)	15.82 (13.95 - 18.87)	11.74 (9.63 - 13.62)	<0.0001
Fms Related Tyrosine Kinase-4 / Vascular endothelial growth factor receptor 3 (ng/ml)	76.4 (70.4 - 81.65)	60.9 (58.4 - 63.4)	<0.0001
Toll like receptor type 2 (ng/ml)	8.53 (8.18 - 9.14)	6.1 (5.67 - 7.07)	<0.0001
E-selectin (ng/ml)	1120 (575.3 – 1944)	839 (528.4 – 1187)	0.024
<b><i>Stress molecules</i></b>			
Hypoxia inducible factor type 1 (fold	2.23 (1.65 - 3.22)	0.9 (0.69 - 1.33)	<0.0001

expression)			
Heat shock protein 70 (ng/ml)	18.86 (14.74 - 33.24)	7.11 (5.95 - 8.03)	<0.0001
<b><i>Cytokines and chemokines</i></b>			
Interleukin-1 $\alpha$ (ng/ml)	0.21 (0.04 - 0.68)	0.11 (0.03 - 0.23)	0.307
Interleukin-1 $\beta$ (ng/ml)	6.68 (3.14 - 9.22)	3.71 (2.55 - 5.55)	0.006
Interleukin-4 (ng/ml)	2.27 (1.33 - 3.04)	1.6 (1.19 - 1.92)	0.003
Interleukin-6 (ng/ml)*	0.08 (0.04 - 0.27)	0.02 (0.01 - 0.09)	0.149
Interleukin-8 (ng/ml)	0.72 (0.26 - 2.01)	0.39 (0.19 - 2.04)	0.720
Interleukin-10 (ng/ml) <sup>†</sup>	10.27 (5.73 - 17.47)	6.16 (4.11 - 8.2)	0.0006
Interleukin-12p70 (ng/ml) <sup>‡</sup>	0.24 (0.13 - 0.44)	0.10 (0.06 - 0.19)	0.006
Interleukin-13 (ng/ml)	0.65 (0.38 - 0.82)	0.47 (0.32 - 0.53)	0.002
Interleukin-17A (ng/ml) <sup>§</sup>	0.47 (0.30 - 0.61)	0.31 (0.23 - 0.38)	0.007
Interferon- $\alpha$ (ng/ml) <sup>  </sup>	0.25 (0.15 - 0.37)	0.14 (0.083 - 0.23)	0.052
Interferon- $\gamma$ (ng/ml) <sup>#</sup>	9.31 (4.39 - 14.13)	4.39 (2.64 - 6.25)	0.009
Tumour necrosis factor- $\alpha$ (ng/ml)	0.60 (0.36 - 1.22)	0.29 (0.21 - 0.54)	0.041
Latency associated protein (ng/ml)	68.6 (43.68 - 121.9)	38.06 (27.33 - 63.64)	0.044



Granulocyte-colony stimulating factor (ng/ml)**	0.16 (0.07 - 0.38)	0.06 (0.03 - 0.19)	0.042
Monocyte chemoattractant protein-1 (ng/ml)	0.31 (0.19 - 0.45)	0.33 (0.21 - 0.44)	0.309
Interferon- $\gamma$ -induced protein 10 (ng/ml)	0.15 (0.11 - 0.26)	0.14 (0.10 - 0.19)	0.105
Macrophage inflammatory protein-1 $\alpha$ (ng/ml) <sup>††</sup>	0.55 (0.36 – 1.53)	0.38 (0.24 – 1.24)	0.176
Macrophage inflammatory protein-1 $\beta$ (ng/ml)	0.56 (0.25 – 1.09)	0.28 (0.16 – 1.25)	0.284

87 \* IL-6, not in detectable concentration in 3 HAP and 12 SLP samples.

88 † IL-10, not in detectable concentration in 1 HAP sample.

89 ‡ IL-12p70, not in detectable concentration in 5 HAP and 4 SLP samples.

90 § IL-17A, not in detectable concentration in 2 HAP samples.

91 ¶ IFN- $\alpha$ , not in detectable concentration in 8 HAP and 6 SLP samples.

92 # IFN- $\gamma$ , not in detectable concentration in 4 HAP samples.

93 \*\* GCSF, not in detectable concentration in 2 SLP samples.

94 †† MIP-1 $\alpha$ , not in detectable concentration in 1 HAP sample.

95 Comparative expression of platelet activation, endothelial cell activation, stress, and  
96 inflammatory molecules in the VTE patients from HA and sea levels. Data is presented in

97 median (IQR) or number (%). Abbreviations are: HAP, VTE patients from HA (study cases);  
 98 SLP, VTE patients from closer to sea level (study controls).

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100 **Table S2. Detailed cutoff threshold values for the parameters investigated.**

Parameter	Threshold/Cutoff value *	Altered condition	Threshold criteria
<b><i>Hematology</i></b>			
Hemoglobin (mg/dl)	16·98 mg/dl	>16·98 mg/dl	90 <sup>th</sup> percentile of SLP
Red blood cells (x10 <sup>6</sup> /ml)	5·94x10 <sup>6</sup> / ml	>5·94x10 <sup>6</sup> / ml	90 <sup>th</sup> percentile of SLP
Platelets (x10 <sup>6</sup> /Cumm)	278x10 <sup>3</sup> /Cumm	>278x10 <sup>3</sup> /Cumm	90 <sup>th</sup> percentile of SLP
Total leucocyte count	8240 counts /ml	>8240 counts/ml	90 <sup>th</sup> percentile of SLP
<b><i>Lipid profile</i></b>			
Total cholesterol (mg/dl)	260·80 mg/dl	>260·80 mg/dl	90 <sup>th</sup> percentile of SLP
Triglyceride (mg/dl)	385·40 mg/dl	>385·40 mg/dl	90 <sup>th</sup> percentile of SLP
High density lipoprotein (mg/dl)	29·20 mg/dl	<29·20 mg/dl	10 <sup>th</sup> percentile of SLP
Low density lipoprotein (mg/dl)	129·60 mg/dl	>129·60 mg/dl	90 <sup>th</sup> percentile of SLP

<b><i>Coagulation profile</i></b>			
Prothrombin time (s)	13·26 s	<13·26 s	10 <sup>th</sup> percentile of SLP
Activated partial thromboplastin time (s)	35·50 s	<35·50 s	10 <sup>th</sup> percentile of SLP
Thrombin time (s)	18·20 s	<18·20 s	10 <sup>th</sup> percentile of SLP
Fibrinogen (mg/ml)	356·4 mg/dl	>356·4 mg/dl	90 <sup>th</sup> percentile of SLP
D-dimer (mg/l)	1·10mg/l	>1·10 mg/l	90 <sup>th</sup> percentile of SLP
VWF Antigen (%)	163 %	>163 %	90 <sup>th</sup> percentile of SLP
Thrombin-anti-thrombin complex (ng/ml)	0·19 ng/ml	>0·19 ng/ml	90 <sup>th</sup> percentile of SLP
Plasmin-anti-plasmin complex (ng/ml)	0·41 ng/ml	>0·41 ng/ml	90 <sup>th</sup> percentile of SLP
<b><i>Thrombophilia profile</i></b>			
Protein C (%)	19·60 %	<19·60 %	10 <sup>th</sup> percentile of SLP
Protein S (%)	26·60 %	<26·60 %	10 <sup>th</sup> percentile of SLP
Antithrombin (%)	45·80 %	<45·80 %	10 <sup>th</sup> percentile of SLP
Factor V (%)	137 %	>137 %	90 <sup>th</sup> percentile of SLP
Factor VII (%)	129·40 %	>129·40 %	90 <sup>th</sup> percentile of SLP
Factor VIII (%)	131·20 %	>131·20 %	90 <sup>th</sup> percentile of SLP
Factor X (%)	140·40 %	>140·40 %	90 <sup>th</sup> percentile of SLP

Activated protein C Resistance (Positive)	Positive	Positive	Positive
Lupus anti-coagulant deficiency (Positive)	Positive	Positive	Positive
<b><i>Platelet activation molecules</i></b>			
CD40 Ligand (ng/ml)	7·39 ng/ml	>7·39 ng/ml	90 <sup>th</sup> percentile of SLP
P-selectin (ng/ml)	103·60 ng/ml	>103·60 ng/ml	90 <sup>th</sup> percentile of SLP
Platelet factor 4 (ng/ml)	58·04 ng/ml	>58·04 ng/ml	90 <sup>th</sup> percentile of SLP
<b><i>Endothelial cell activation molecules</i></b>			
Intracellular adhesion molecule type-1 (ng/ml)	47·01 ng/ml	>47·01 ng/ml	90 <sup>th</sup> percentile of SLP
Vascular cell adhesion molecule type - 1 (ng/ml)	23·32 ng/ml	>23·32 ng/ml	90 <sup>th</sup> percentile of SLP
Vascular endothelial growth factor (ng/ml)	16·79 ng/ml	>16·79 ng/ml	90 <sup>th</sup> percentile of SLP
Fms Related Tyrosine Kinase-4 / Vascular endothelial growth factor receptor 3 (ng/ml)	65·75 ng/ml	>65·75 ng/ml	90 <sup>th</sup> percentile of SLP

Toll like receptor type 2 (ng/ml)	7·86 ng/ml	>7·86 ng/ml	90 <sup>th</sup> percentile of SLP
E-selectin (ng/ml)	1452 ng/ml	>1452 ng/ml	90 <sup>th</sup> percentile of SLP
<b><i>Stress molecules</i></b>			
Hypoxia inducible factor type 1 (fold expression)	1·50 fold	>1·50 fold	90 <sup>th</sup> percentile of SLP
Heat shock protein 70 (ng/ml)	9·96 ng/ml	>9·96 ng/ml	90 <sup>th</sup> percentile of SLP
<b><i>Cytokines and chemokines</i></b>			
Interleukin-1 $\alpha$ (ng/ml)	1·12 ng/ml	>1·12 ng/ml	90 <sup>th</sup> percentile of SLP
Interleukin-1 $\beta$ (ng/ml)	9·26 ng/ml	>9·26 ng/ml	90 <sup>th</sup> percentile of SLP
Interleukin-4 (ng/ml)	0·50ng/ml	<0·50ng/ml	10 <sup>th</sup> percentile of SLP
Interleukin-6 (ng/ml)	0·23ng/ml	>0·23ng/ml	90 <sup>th</sup> percentile of SLP
Interleukin-8 (ng/ml)	6·52ng/ml	>6·52ng/ml	90 <sup>th</sup> percentile of SLP
Interleukin-10 (ng/ml)	1·95 ng/ml	<1·95 ng/ml	10 <sup>th</sup> percentile of SLP
Interleukin-12p70 (ng/ml)	0·39ng/ml	>0·39ng/ml	90 <sup>th</sup> percentile of SLP
Interleukin-13 (ng/ml)	0·19ng/ml	<0·19ng/ml	10 <sup>th</sup> percentile of SLP
Interleukin-17A (ng/ml)	0·68ng/ml	>0·68ng/ml	90 <sup>th</sup> percentile of SLP
Interferon- $\alpha$ (ng/ml)	0·42ng/ml	>0·42ng/ml	90 <sup>th</sup> percentile of SLP

Interferon- $\gamma$ (ng/ml)	14·70 ng/ml	>14·70 ng/ml	90 <sup>th</sup> percentile of SLP
Tumour necrosis factor- $\alpha$ (ng/ml)	1·18ng/ml	>1·18ng/ml	90 <sup>th</sup> percentile of SLP
Latency associated protein (ng/ml)	20·65 ng/ml	<20·65 ng/ml	10 <sup>th</sup> percentile of SLP
Granulocyte-colony stimulating factor (ng/ml)	0·54ng/ml	>0·54ng/ml	90 <sup>th</sup> percentile of SLP
Monocyte chemoattractant protein-1 (ng/ml)	0·60ng/ml	>0·60ng/ml	90 <sup>th</sup> percentile of SLP
Interferon- $\gamma$ -induced protein 10 (ng/ml)	0·24ng/ml	>0·24ng/ml	90 <sup>th</sup> percentile of SLP
Macrophage inflammatory protein-1 $\alpha$ (ng/ml)	2·04ng/ml	>2·04ng/ml	90 <sup>th</sup> percentile of SLP
Macrophage inflammatory protein-1 $\beta$ (ng/ml)	3·33ng/ml	>3·33ng/ml	90 <sup>th</sup> percentile of SLP

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102 \*Cutoff/Threshold for this study. The threshold was defined as 90<sup>th</sup> percentile of the values in

103 SLPs for the up-expressed variables and 10<sup>th</sup> percentile of the values in SLPs for the down-

104 expressed variables. SLP, VTE patients from closer to sea level (study controls).

**Table S3. Sensitivity and specificity for platelet and endothelial activation marker molecules depicting the association of molecules with VTE incidences at HA.**

<b>Parameters</b>	<b>AUC (95%CI)</b>	<b><i>P</i></b>	<b>Sensitivity %, (95% CI)</b>	<b>Specificity %, (95% CI)</b>
CD40L	0·90 (0·84 - 0·96)	<0·0001	76 (62 – 86)	89 (76 – 96)
P-selectin	0·79 (0·7 - 0·88)	<0·0001	34 (22 – 48)	91 (79 – 98)
PF4	0·9 (0·84 - 0·96)	<0·0001	81 (68 – 91)	91 (79 – 98)
ICAM1	0·86 (0·79 - 0·93)	<0·0001	57 (42 – 70)	91 (79 – 98)
VCAM1	0·97 (0·95 - 0·99)	<0·0001	85 (72 – 93)	91 (79 – 98)
VEGF	0·87 (0·8 - 0·94)	<0·0001	45 (32 – 60)	89 (76 – 96)
FLT4	0·94 (0·89 - 0·99)	<0·0001	87 (75 – 95)	87 (73 – 95)
TLR2	0·98 (0·96 – 1·0)	<0·0001	94 (84 – 99)	89 (76 – 96)
E-selectin	0·62 (0·5 - 0·73)	0·05	35 (22 – 50)	91 (79 – 98)

Table presents the sensitivity and specificity satisfying the discrimination between VTE incidences at high altitudes and sea level in the terms of platelet and endothelial cell activation markers. AUC, area under curve; CI, confidence interval; CD40L, CD40 ligand; PF4, platelet factor 4; ICAM1, intracellular adhesion molecule 1; VCAM1, vascular cell adhesion molecule 1;

114 VEGF, vascular endothelial growth factor; FLT4, fms related tyrosine kinase 4 (vascular  
115 endothelial growth factor receptor 3); TLR2, toll like receptors 2.

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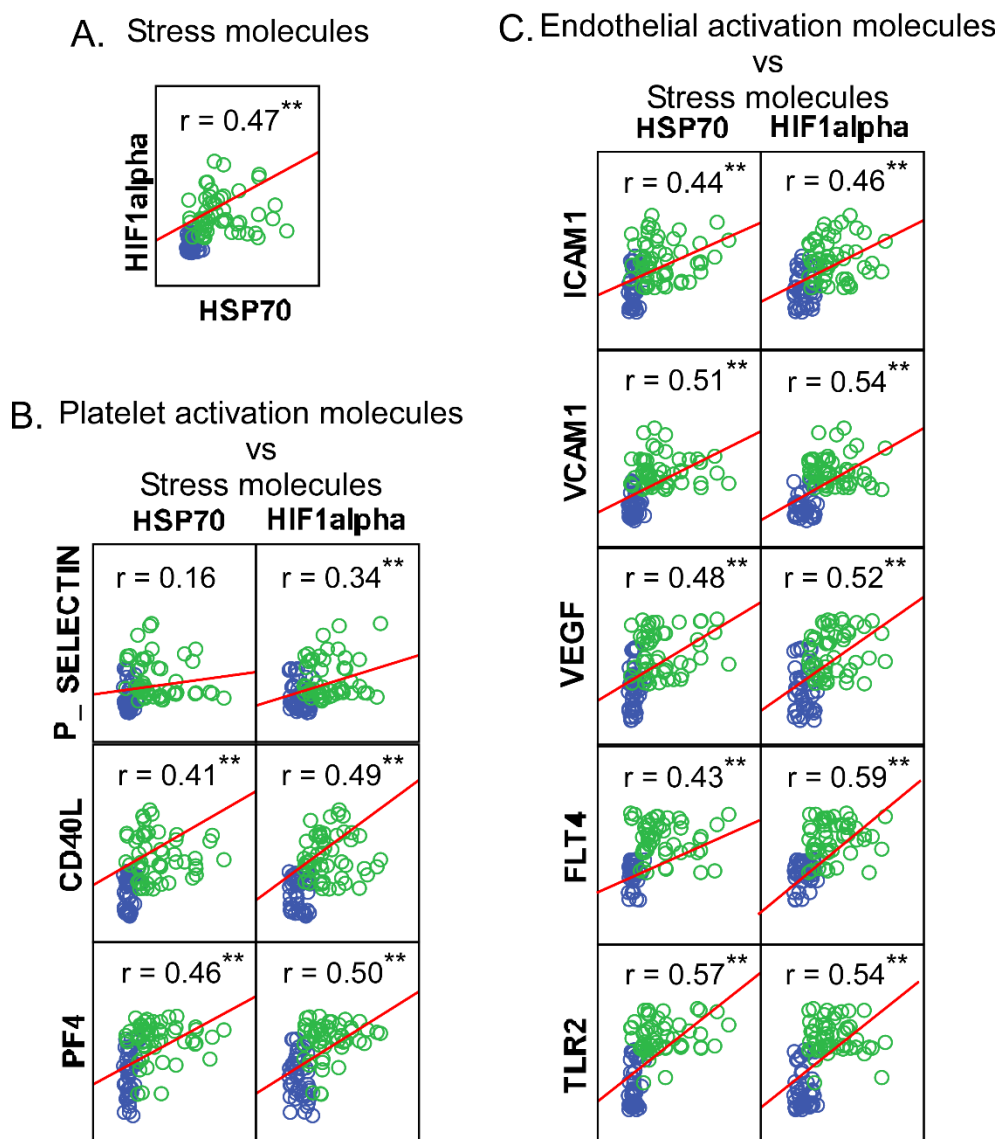
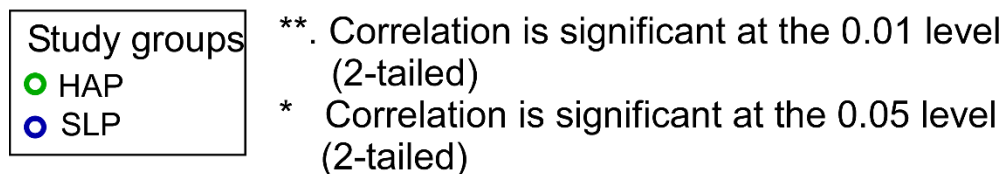
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121 **SUPPLEMENTAL FIGURES:**

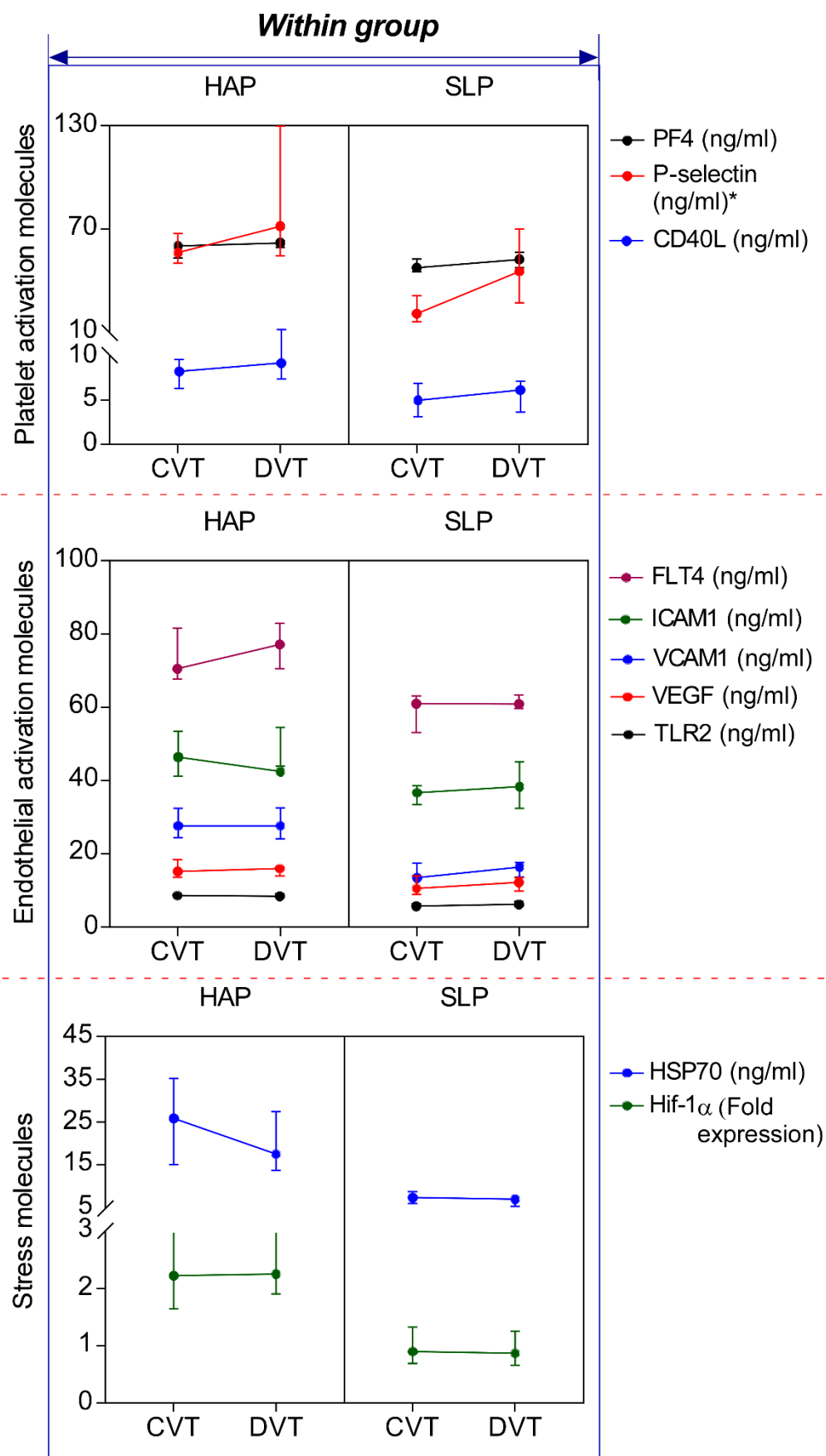




**Figure S1. Correlation of stress molecules with platelet and endothelial activation molecules.** HAP, VTE patients from HA (study cases); SLP, VTE patients from closer to sea level (study controls); HIF-1 $\alpha$ , hypoxia inducible factor 1 alpha; HSP70, heat shock protein 70; CD40L, CD40 ligand; PF4, platelet factor 4; ICAM1, intracellular adhesion molecule 1,

127 VCAM1; vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; FLT4,  
128 Fms Related Tyrosine Kinase 4 (or vascular endothelial growth factor receptor 3/VEGFR3);  
129 TLR2, toll like receptor 2.

130



132 **Figure S2. Within the group comparison of platelet, endothelial, and stress marker**  
133 **molecules.** Differences in the plasma concentration of platelet, endothelial activation, and stress  
134 molecules. P-selectin was the only molecule which showed significant difference in the  
135 expression between DVT and CVT in both the study groups ( $*P<0.05$ ). HAP, VTE patients from  
136 HA (study cases); SLP, VTE patients from closer to sea level (study controls); DVT, deep vein  
137 thrombosis; CVT, cerebral venous thrombosis.